MECHANISM OF ACTION OF NONACHLAZINE ON NERVOUS CONTROL OVER THE CORONARY CIRCULATION

É. A. Bendikov and T. S. Gan'shina

UDC 615.224:547.869.2.
015.4:612.172.1

The new antiaginal drug nonachlazine, in experiments on anesthetized cats and dogs, inhibited the response of reflex decrease of the blood flow into the coronary arteries. In freely behaving cats nonachlazine also inhibited reflex changes in the blood flow in the system of the common carotid artery and reduced pressor vasomotor reflexes. Nonachlazine selectively inhibited vasoconstrictor impulses from Aδ-afferent fibers of spinal nerves, i.e., it acts on the vasomotor component of the "primary" nociceptive response. This mechanism may perhaps lie at the basis of the relief of the pain syndrome by nonachlazine in ischemic heart disease.
KEY WORDS: *vasomotor control; coronary circulation; nonachlazine.*

The results of a clinical trial of the new antianginal drug nonachlazine, synthesized and investigated pharmacologically at the Institute of Pharmacology, Academy of Medical Sciences of the USSR [6, 7], indicate that the substance is very effective in patients with ischemic heart disease [3].

This paper describes an experimental analysis of the effect of nonachlazine on nervous control of the coronary circulation and of the role of the central component in the mechanism of its antianginal action.

EXPERIMENTAL METHOD

Experiments were carried out on 20 cats and eight dogs. In the experiments of series I, the animals were anesthetized with urethane and chloralose and artificially ventilated, and changes in the blood flow into the circumflex branch of the left coronary artery [9] were recorded in response to electrical stimulation of A- and C-afferent fibers of the tibial nerve. The "Nicotron" electromagnetic flowmeter was used.

In the experiments of series II, changes in the blood flow in the common carotid artery and changes in arterial pressure in response to electrical stimulation of an area of skin of the thigh (3-15 V, 2-16 stimuli/sec) were recorded in freely behaving cats after preliminary implantation of an electromagnetic sensor.

In series III, changes in tonic activity and reflex responses in the sympathetic nerves of the heart to stimulation of the A- or A- and C-groups of afferent fibers of the tibial nerve (1-2 and 4-20 stimuli/sec) were recorded under general anesthesia [2]. The flow of blood into the coronary artery was recorded on the Mingograph-81 (Elema) apparatus. Nonachlazine was injected intravenously in doses of 5-7 mg/kg.

EXPERIMENTAL RESULTS AND DISCUSSION

The afferent system of the A- and C-groups of spinal nerves are known to play an important role in vasoconstrictor reflexes [11]. In experiments on cats during stimulation of the tibial nerve (5 V, 16 stimuli/sec; six experiments) the coronary blood flow was

Laboratory of Pharmacology of the Cardiovascular System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 81, No. 3, pp. 319-322, March, 1976. Original article submitted September 19, 1975.

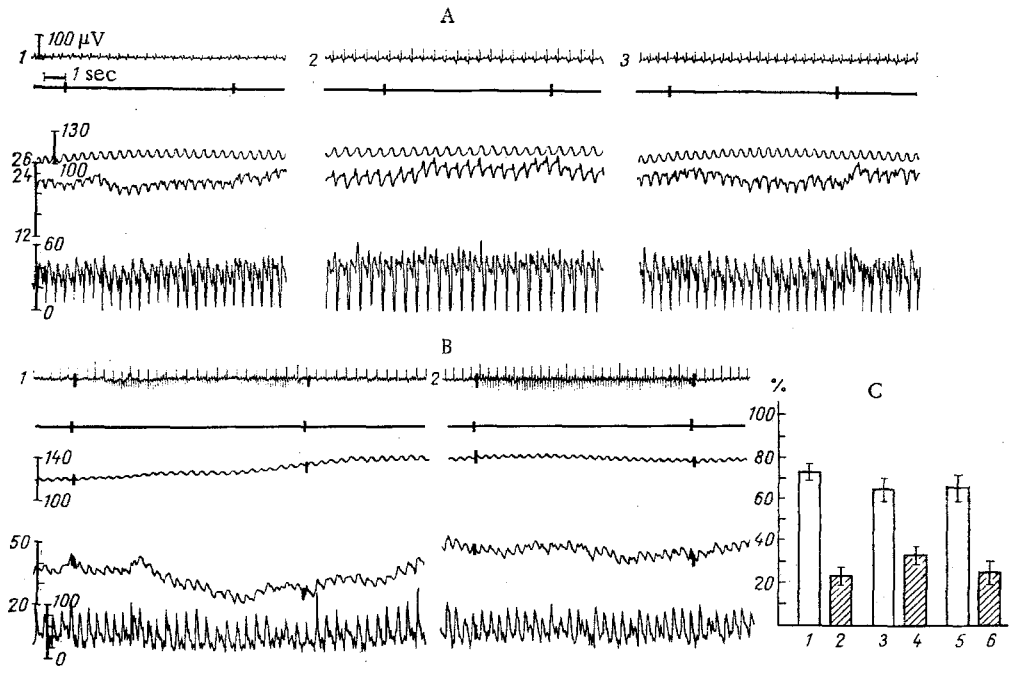

Fig. 1. Effect of nonachlazine on reflex changes in blood flow in systems of coronary (A, C) and carotid (B, C) arteries. A) From top to bottom: ECG, marker of tibial nerve stimulation (5 V, 16 stimuli/sec); arterial pressure (in mm Hg); averaged and phasic blood flow in circumflex branch of left coronary artery of dog (in ml/min). 1) Control; 2 and 3) 15 and 50 min respectively after intravenous injection of nonachlazine (5 mg/kg). B) Changes in blood flow into system of common carotid artery of cat under conditions of free behavior. Legend as in A. C) Degree of inhibition by nonachlazine of reflex decrease in blood flow in coronary (1-4) and carotid (5, 6) arteries: 1, 2) in dogs; 3, 4) in anesthetized cats; 5, 6) in freely behaving cats. Unshaded columns 5 V, 16 stimuli/sec; shaded columns 15 V, 16 stimuli/sec.

reduced on the average by 18.5±0.99%, and in experiments on dogs by 21.2±1.3% (5 V, 16 stimuli/sec; seven experiments) and 30.6±1.9% (15 V, 16 stimuli/sec; eight experiments). Within 5-10 min after injection, nonachlazine considerably inhibited the response of the coronary blood flow to electrical stimulation, and in some cases it led to a reflex increase in the blood flow into the coronary vessels (Fig. 1A). The coronary and systemic vasomotor reflexes from fast-conducting and high-threshold group A fibers of the tibial nerve (3-5 V, 0.1-1 msec, 4-16 stimuli/sec) were evidently more sensitive to nonachlazine than vascular responses to stimulation of all the afferent fibers, including slowly conducting and high-threshold afferent fibers of group C (15-30 V, 1 msec, 4-16 stimuli/sec) (Fig. 1C). In dogs, in particular, pressor reflexes to stimulation at 5 V, 16 stimuli/sec were inhibited by the drug to the extent of 75±1.6%, whereas in response to stimulation at 15 V, 16 stimuli/sec, inhibition was by only 23.16±1.5%.

Similar results were obtained in cats under conditions of free behavior (Fig. 1B, C). In these experiments nonachlazine inhibited the response of a reflex decrease in blood flow and the pressor reflex on the average by 64.8±2.2 and 64.6±2.7% respectively during stimulation at 5 V, 16 stimuli/sec, and stimulation at 15 V, 16 stimuli/sec by only 24.6± 1.9% and 25.6±2.7% respectively.

The experiments of series III showed that during stimulation of group A afferent fibers of the tibial nerve within the range of physiological frequencies of sympathetic impulse trains (1-2 stimuli/sec) [10], nonachlazine did not inhibit tonic activity or responses in the inferior cardiac nerve (Fig. 2B). Nonachlazine likewise did not change summation of impulses from afferent group C fibers, as is characteristic of analgesics of the morphine group [4]. However, in response to stimulation of the tibial nerve at a

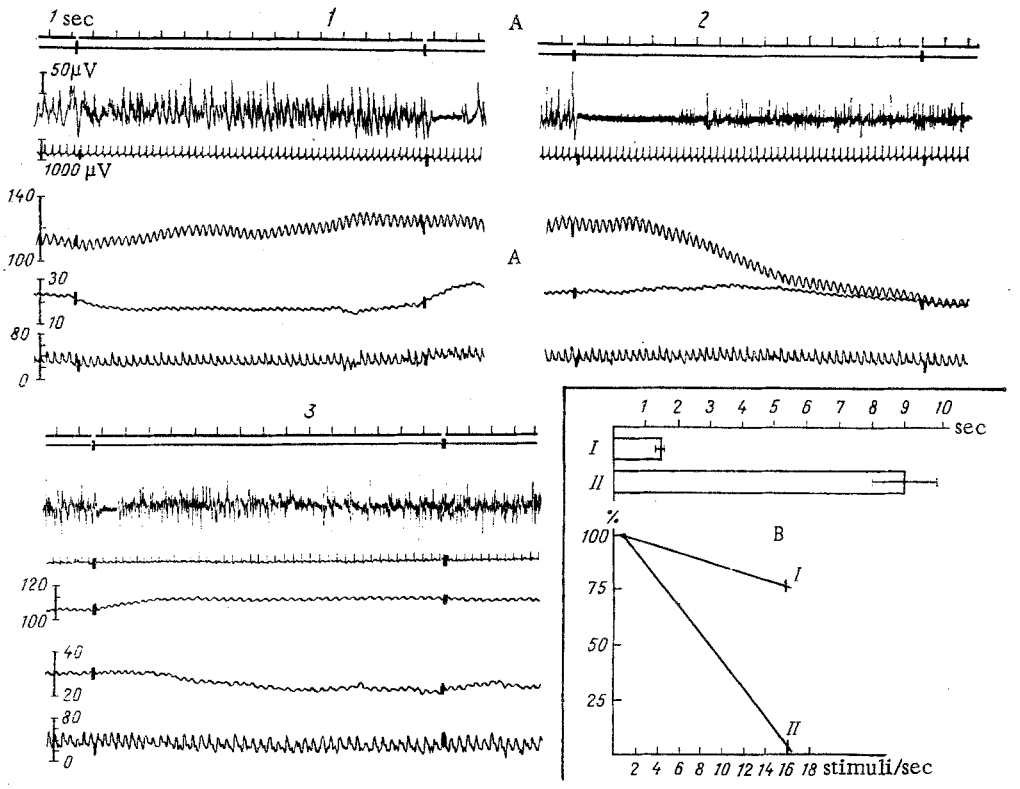

Fig. 2. Increase in intensity of inhibition of reflex responses in sympathetic nerve of heart to stimulation of A-group of afferent fibers of tibial nerve by nonachlazine. In A — legend as in Fig. 1A; top — tonic activity and reflex responses in inferior cardiac nerve, bottom — reflex changes in blood flow in common carotid artery (to stimulation at 5 V, 20 stimuli/sec). Top graph in B shows duration of inhibition of reflex responses (in sec); bottom graph shows intensity of inhibition of averaged high-amplitude spikes in responses from group A afferents to stimulation with frequencies of 1 and 16 stimuli/sec. I) Control; II) after injection of nonachlazine (7 mg/kg).

frequency of 4-20 stimuli/sec and with a strength of 5 V, when the whole spectrum of Aδ-afferent fibers was excited and a vasomotor component of "primary" pain was formed (a reflex decrease in the blood flow in the systems of the coronary and carotid arteries), nonachlazine completely or considerably inhibited responses from group A afferent fibers and substantially modified the character of the vascular reflexes (Fig. 2A). This effect of nonachlazine can be considered to be the result of strengthening of central inhibitory processes [8, 11]. This conclusion is confirmed by the fact that after application of a series of stimuli triggering an inhibitory response to the tibial nerve, subsequent stimuli with a frequency of 16-20/sec did not induce corresponding reflex responses from Aδ-afferent fibers in the cardiac sympathetic nerve (Fig. 2A, B).

Nonachlazine thus has an effect on the central mechanisms of regulation of the coronary circulation. Differences in the sensitivity of the vascular reflexes from different afferent systems to nonachlazine permit the mechanism of its cardiovascular effects to be examined from the standpoint of the synaptic theory of action of pharmacological substances [4]. The effect of this drug, like that of nitroglycerine, is evidently due to blockage of the constrictor responses of the coronary vessels to impulses from the Aδ-afferent fibers of the spinal nerves which form the vasomotor component of the "primary" nociceptive response [1-5]. It must be emphasized that nonachlazine does not change the physiological parameters of nervous regulation of vascular tone, but it is effective under the conditions of the nociceptive response to high-frequency stimulation of afferent fibers. It could be that the effect of nonachlazine on the pain syndrome in ischemic heart disease is connected with precisely these properties.

LITERATURE CITED

1. É. A. Bendikov, in: The Neuronal Mechanisms of Pain (Proceedings of an All-Union Symposium) [in Russian], Leningrad (1972), pp. 76-78.
2. É. A. Bendikov and V. G. Butuzov, in: The Pharmacology of Monoaminergic Processes [in Russian], Moscow (1971), pp. 24-78.
3. G. A. Dubova, R. G. Davydova, and G. A. Markova, Klin. Med., No. 10, 47 (1974).
4. V. V. Zakusov, The Pharmacology of Central Synapses [in Russian], Moscow (1973).
5. N. V. Kaverina and É. A. Bendikov, Farmakol. i. Toksikol., No. 2, 218 (1973).
6. N. V. Kaverina, É. A. Bendikov, G. A. Markova, et al., in: Symposium on Blockers of β-adrenergic Receptors [in Russian], Moscow (1973), p. 15.
7. N. V. Kaverina and G. A. Markova, in: Farmakol. i Toksikol., No. 2, 173 (1975).
8. V. A. Tsyrlin and V. S. Gerasimenko, in: The Pharmacological Study of Hypotensive Agents with Central Action [in Russian], Leningrad (1975), pp. 44-58.
9. G. D. Buckberg and G. Ross, Cardiovasc. Res., 7, 429 (1973).
10. B. Folkow, Acta Physiol. Scand., 25, 49 (1952).
11. A. Sato and R. F. Schmidt, Physiol. Rev., 53, 916 (1973).